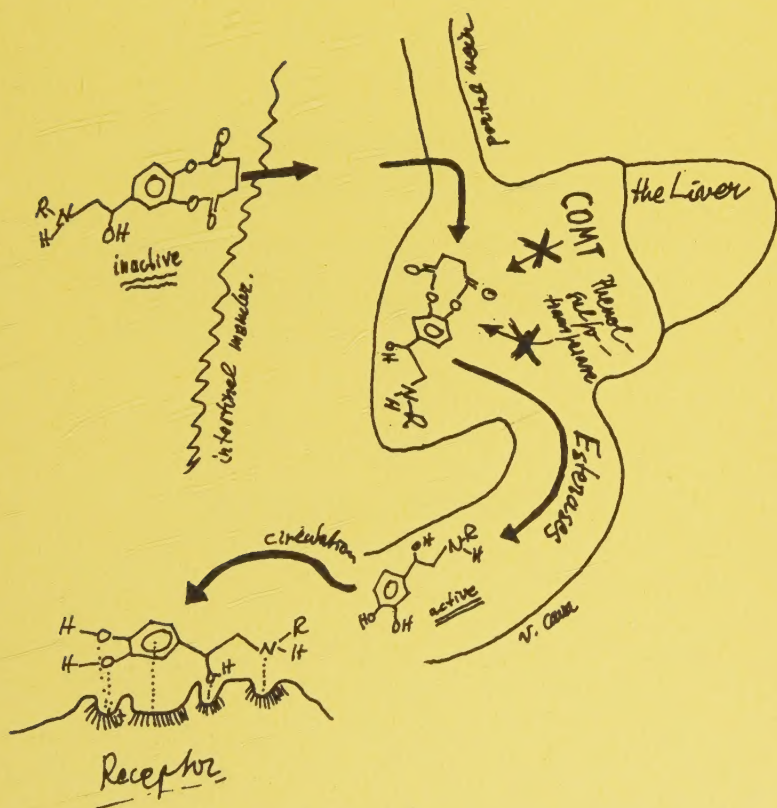


DRUG LATENTIATION

STUDIES ON CATECHOL ESTERS OF
CERTAIN DIACIDS

by

LEIF-ÅKE SVENSSON



Department of Organic Chemistry, Chemical Center,
University of Lund, Lund, Sweden and
Research Laboratories of AB Draco, Lund, Sweden

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CERTAIN DIACIDS

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Drug latention

Studies on catechol esters of certain diacids

Leif-Åke Svensson

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University of Lund, Sweden and

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Lund, Sweden

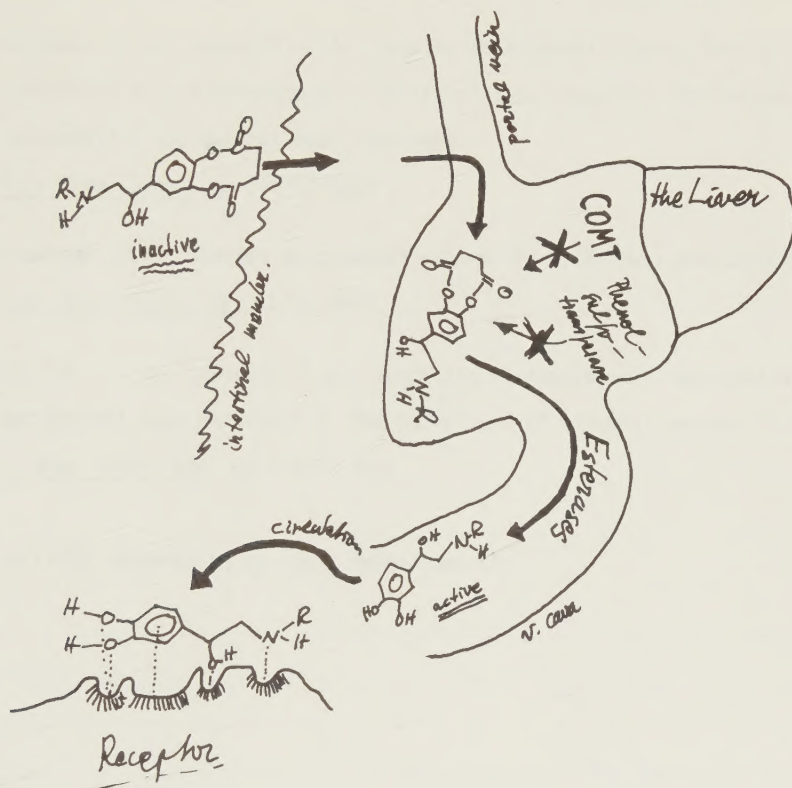


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This thesis is a summary of the following papers:

- I. Svensson, L.Å., Studies on catechol esters. Part I.
Synthesis of cyclic succinoylcatechols and o-hydroxyphenyl acid succinates.
Acta Chem. Scand. 26 (1972) 0000
- II. Eberson, L. and Svensson, L.Å., Studies on catechol esters. Part II.
Hydrolysis of cyclic succinoylcatechols.
Acta Pharm. Suecica 9 (1972) 0000
- III. Eberson, L. and Svensson, L.Å., Studies on catechol esters. Part III.
Hydrolysis of o-hydroxyphenyl acid succinates: Competing intramolecular nucleophilic and general base catalysis.
Acta Chem. Scand. 26 (1972) 0000
- IV. Svensson, L.Å., Studies on catechol esters. Part IV. Mass spectrometry.
Acta Chem. Scand. 26 (1972) 0000
- V. Eberson, L. and Svensson, L.Å.: Competing intramolecular nucleophilic and general base catalysis in the hydrolysis of catechol monosuccinates.
J. Amer. Chem. Soc. 93 (1971) 3827

These papers will be referred to by their Roman numerals.

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Abstract

Some synthetic routes to cyclic succinoylcatechols, 3,4-dihydro-1,6-benzodioxocin-2,5-diones, 4, are described together with the synthesis of a series of o-hydroxyphenyl acid succinates, 12. Compounds 4 are best prepared by Baeyer-Villiger oxidation of 1,2,3,4-tetrahydro-1,4-naphthalene-diones, 8, or of ϵ -lactones of β -(o-hydroxybenzoyl) propionic acids, 9, with peroxy trifluoroacetic acid. Also, the direct condensation of catechol with an appropriate succinoyl chloride in the presence of base is, in certain cases, applicable for the synthesis of 4. Compounds 12 are prepared by reaction of catechol monoanion with a suitable succinic anhydride.

The mass spectrometric behavior of compounds 4 and the corresponding catechol diacetates have been compared, and it has been found, that except for processes due to losses of CO and CO₂ from the molecular ions of 4, the fragmentation patterns of 4 and the catechol diacetates are essentially of the same type.

Mass spectrometric analysis of the trimethylsilyl derivatives of compounds 12 has also been performed, and a rearrangement involving the trimethylsilyl group has been observed.

Complete pH-rate profiles for the hydrolysis of compounds 4 and 12 have been determined at 25.0°C in water containing 11% (by volume) acetonitrile.

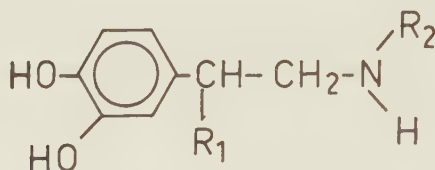
For compound 4 it has been found that the hydrolysis takes place in accordance with the $\text{B}_{\text{AC}}2$ mechanism for ester hydrolysis with much higher rates than those found for their non-cyclic analogues, i.e. catechol diacetates. Possible explanations for this behavior are discussed.

Compounds 12 have been found to undergo hydrolysis by a competing intramolecular nucleophilic and general base catalyzed mechanism, i.e.: at values of pH below 8 hydrolysis takes place via intramolecular carboxylate ion catalysis, whereas at values of pH above ca. 8 a change in mechanism to intramolecular general base catalysis from the adjacent ortho phenolate group is recognizable and, when the latter mechanism is operating, the first mechanism becomes depressed, due to electrostatic repulsion in the dianion of 12.

Introduction

There are many examples in the chemistry of the human body where a compound, after once having exerted its proper and specific action, is transformed by means of enzymatic reactions into one or several inactive derivatives. Such inactivation reactions usually lead to easily excretable derivatives, which are eliminated from the body via either the liver (bile, faeces) or the kidneys (urin).

In the metabolism of circulating adrenaline, 1c, (and other catecholamines, e.g. 1) it has been established that inactivation takes place by O-methylation and/or O-sulphatation in



1a $R_{1,2} = H$: Dopamine

1b $R_1 = OH$ $R_2 = H$: Noradrenaline

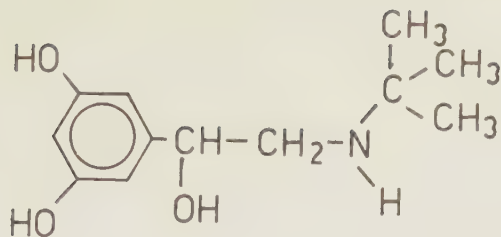
1c $R_1 = OH$ $R_2 = Me$: Adrenaline

1d $R_1 = OH$ $R_2 = -CH \begin{matrix} \nearrow CH_3 \\ \searrow CH_3 \end{matrix}$: Isoprenaline

the 3- and 4-positions of the catechol moiety ¹. These biotransformations take place mainly in the liver, where high concentrations of the proper enzymes, i.e. catechol-O-methyl transferase (COMT) and phenolsulfotransferase ², are available.

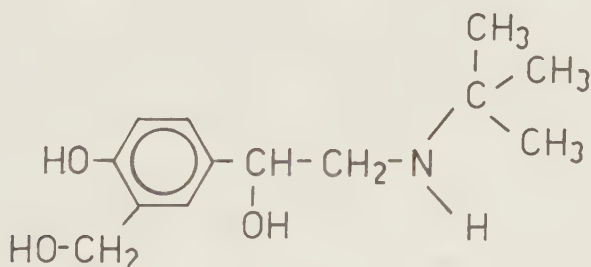
Since the resorption of a drug taken perorally almost exclusively takes place in the small intestine, from where it is brought by the blood to the liver, one immediately sees that for the catecholamines this way of administration is less suitable, because a great part of the drug will rapidly be inactivated by O-conjugation and excreted before having had the possibility of exerting its pharmacological action.

However, since the 3,4-dihydroxyphenyl moiety has been found to be a prerequisite for O-methylation by COMT ³, modification of this structure to the analogue 3,5-dihydroxyphenyl derivatives, e.g. 2, has offered one way to overcome this inactivation reaction ⁴.



2 Terbutaline

Insertion of a methylene group between the hydroxyl group in the 3-position and the benzene ring, e.g. 3⁵, has the same effect: O-methylation of these substrates fails. Instead, these compounds are inactivated and excreted via the O-sulphatation-⁶ resp. O-glucuronidation-⁷ pathways.



3 Salbutamol

But how can a catecholamine be protected from attack by COMT and phenolsulfotransferase without losing the pharmacological properties of the compound?

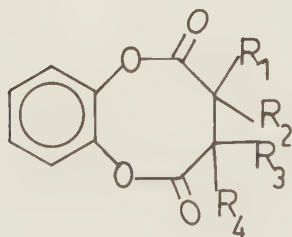
One way to do this may be by blocking the two phenolic hydroxyl groups in the catechol moiety by a suitable functional group, which possibly also may increase the lipophilicity of the compound, making it more easily resorbed in the intestine. Such a blocking group must fulfil at least the following three requirements: 1) it must be stable enough to acid to permit passage through the stomach, 2) it must be relatively easy to split off by means of enzymatic action in the blood plasma, and 3) if there are two blocking groups, both must be split off simultaneously, or almost simultaneously, in order to avoid undesired effects from or excretion of the monosubstituted derivative.

Now, it is known that catechol diacetate is hydrolyzed via a two step mechanism, in which the first step is about 150 times slower than the second one⁸, and it has recently been shown that the rate enhancement in the second step can be explained in terms of intra-

molecular general base catalysis⁹. Catechol diacetate also has the feature of being relatively stable to acid solutions.

Since the ester function is readily hydrolyzed by enzymes and the two ester groups in catechol diacetate are split off at different rates, the ester function would seem to be well suited as a blocking group. Moreover, phenyl acid succinates are known to hydrolyze via intramolecular carboxylate ion catalysis with much higher rates than in the case of general base catalyzed hydrolysis of catechol monoacetate¹⁰. It has also been shown that increased alkyl substitution in the succinic acid moiety, the gem-dialkyl effect, greatly increases the rate of the intramolecularly catalyzed step¹¹. Since the first step in the hydrolysis of catechol diacetate is effected via the $\beta_{AC}2$ -mechanism, increased alkyl substitution in the acid moiety will make the attack at the carbonyl carbon atom more difficult and hence the rate of hydrolysis slower¹².

In line with the discussion above, the work summarized in this thesis has paid special attention to the acyl group, and particularly the succinoyl group, to find out if this group will fulfil the requirements for a blocking group, as stated above. Therefore, a series of cyclic succinoylcatechols, 3,4-dihydro-1,6-benzodioxocin-2,5-diones, 4a - d, have been synthesized as model compounds for the more complicated catecholamine structures (I), in order to study the kinetics of the two steps involved in the hydrolysis of these compounds (Eqn.1).

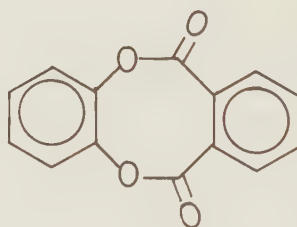


4a $R_{1-4} = H$

c $R_{1-4} = Me$

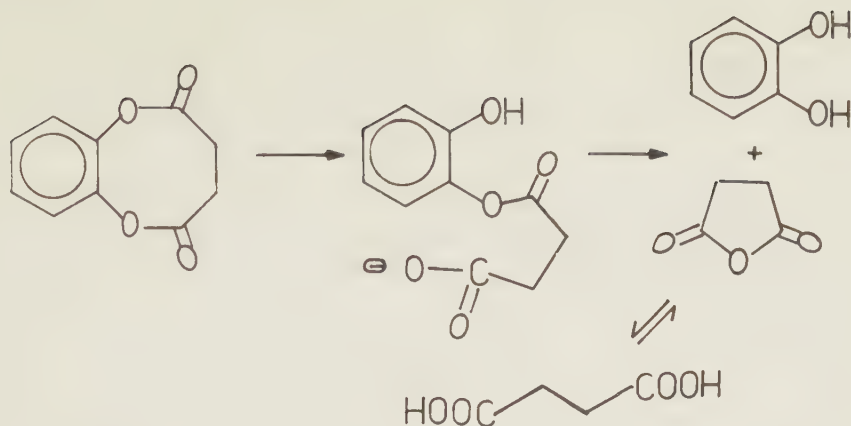
b $R_1 = Me$

$R_2 = H$



4d

One can expect the rate of hydrolysis of the first step in 4a - d to be slowed down by increased alkyl substitution in the succinic acid moiety, which at the same time will greatly increase the rate of the second intramolecularly catalyzed step.



Since it is known from studies on acylation and deacylation reactions of esterases by phenyl acetates¹³ that these reactions follow the normal steric order of reactivity, it is hoped that also the cyclic succinoylcatecholamines will behave similarly in their reactions with esterases.

A. Synthesis and mass spectrometry

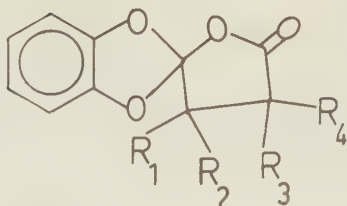
The following methods have been tried for the synthesis of compounds 4a - d (I):

1. Reaction between catechol and the appropriate succinoyl chloride in the presence of pyridine.
2. Condensation of catechol and the appropriate succinic acid in the presence of dicyclohexylcarbodiimide (DCC).
3. Intramolecular condensation of o-hydroxyphenyl acid succinates in the presence of DCC.
4. Baeyer-Villiger oxidation of 1,2,3,4-tetrahydro-1,4-naphthalenediones and ϵ -lactones of β -(o-hydroxybenzoyl)propionic acids.
5. Trichloroisocyanuric acid (TCC)-oxidation of 2,3,4,5-tetrahydro-1,6-benzodioxocin in the presence of water.

The first method, (1), was found to work properly only for the tetramethylsuccinoyl chloride and phthaloyl chloride, which in their reactions with catechol resulted in a low yield (< 5%) of a mixture of the isomeric pseudoester (5b and c) and 4 (c, d).

The formation of compounds like 5 leads one to suspect a ring-chain tautomeric equilibrium of the diacid chloride. For phthaloyl chloride, this behavior has previously been

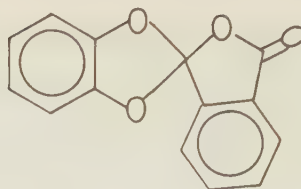
established ¹⁴, but no evidence for such a reaction has been found for succinoyl chloride ¹⁵.



5a $R_{1,3} = H$

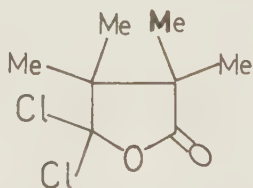
$R_{2,4} = Me$

b $R_{1-4} = Me$



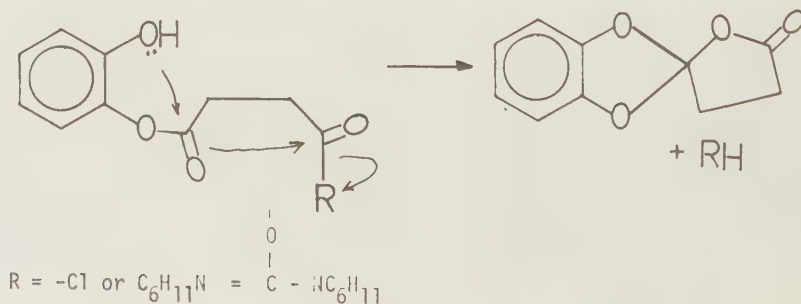
5c

If the gem-dimethyl effect is operating also in the succinoyl chloride series, this effect may stabilize the ring form in a ring-chain tautomeric equilibrium. Thus, it is possible that this reaction will operate in the tetramethylsuccinoyl chloride. In fact, nmr analysis of this compound reveals a small doublet located between the two peaks from the methyl groups in the sym-acid chloride and the anhydride (which is present as an impurity). This doublet may derive from the two pairs of non-equivalent methyl groups in the ring form of the tetramethylsuccinoyl chloride, 6.



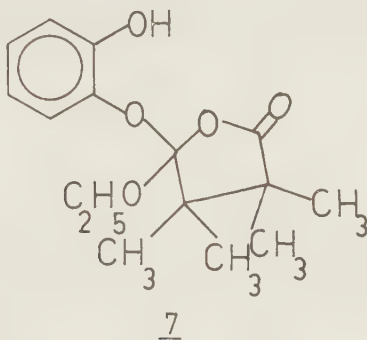
6

However, the mechanism described in Eqn. 2 may also explain the formation of compounds 5 and operate simultaneously with a mechanism involving direct reaction of 6 with catechol.



This mechanism may also be responsible for the formation of 5b in the reaction of o-hydroxyphenyl acid-2,3-dimethylsuccinate with DCC in an attempt to prepare the corresponding dimethyl substituted cyclic succinoylcatechol (method 3). When DCC was used as the condensing agent in the reaction between 2-methyl succinic acid and catechol (method 2) a small amount of 4b was obtained.

The preference for formation of pseudoesters like 5 is further demonstrated in the photolysis of 4c in ethanol solution, where 5b and 7 are the two reaction products formed.

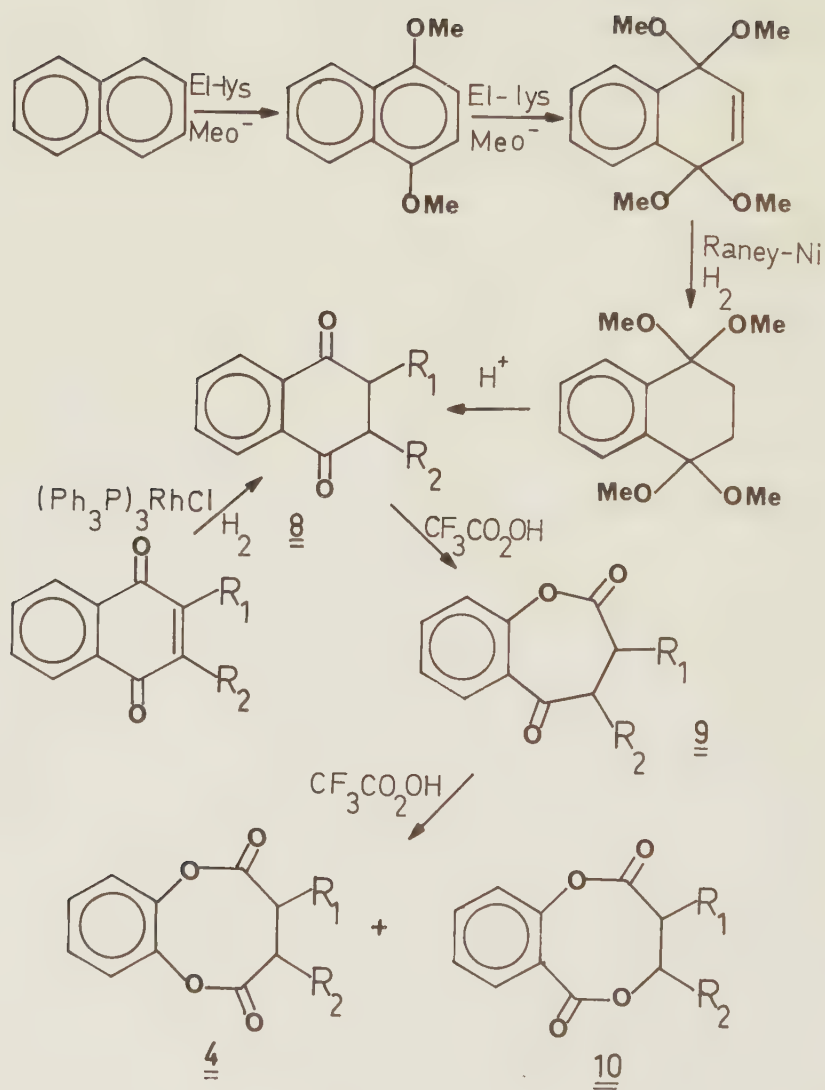


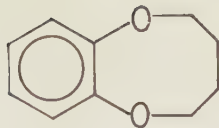
However, the best method for preparation of the cyclic succinoylcatechols 4a, b and d has been found to be Baeyer-Villiger oxidation¹⁶ of 1,2,3,4-tetrahydro-1,4-naphthalene diones, 8, with peroxytrifluoroacetic acid (See Scheme 1). The oxidation of 8 was found to proceed via the ϵ -lactone 9, the preparation of which was also achieved by intramolecular dehydration of the corresponding β -(o-hydroxybenzoyl) propionic acid with DCC.

For the Baeyer-Villiger oxidation reactions of 8, it was found that the migratory aptitudes of different groups was in agreement with previous observations on phenyl alkyl ketones¹⁷. For this reason, the oxidation of both 8 ($R_{1,2}$ = Me) and 9 ($R_{1,2}$ = Me) resulted mainly in formation of the isomeric salicylate 10 (Scheme 1).

Since TCC has been reported to oxidize ethers to esters¹⁸, this reagent was tested on the cyclic ether 11 for the attempted preparation of 4a. However, no ester could be detected but instead, almost quantitative conversion of 11 to its monochlorinated derivative was found to have taken place. The same result was obtained with other substrates, e.g. anisole and phenetole, and this reaction seems to be a convenient route for the monochlorination of activated benzene compounds, as has also recently been reported by Juenge *et al.*¹⁹.

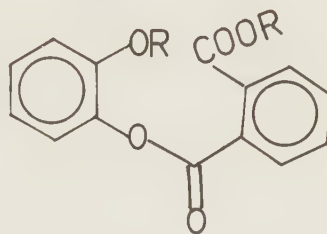
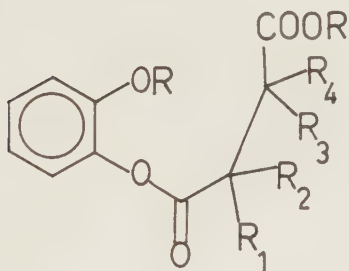
Scheme 1





11

Since difficulties were to be expected in analyzing the kinetics of the two consecutive steps in the hydrolysis of compounds 4 (see Eqn. 1), the corresponding o-hydroxyphenyl acid succinates 12a - h (R = H) were also synthesized (I) in order to investigate their hydrolytic behavior (III and V).



12a a R₁₋₄ = H

d R_{1,3} = H (dl)

12h

b R₁ = Me

R_{2,4} = Me

R₂₋₄ = H

e R_{1,3} = H (meso)

(R = H or TMS)

c R_{1,2} = Me

R_{2,4} = Me

R_{3,4} = H

f R₁₋₃ = Me

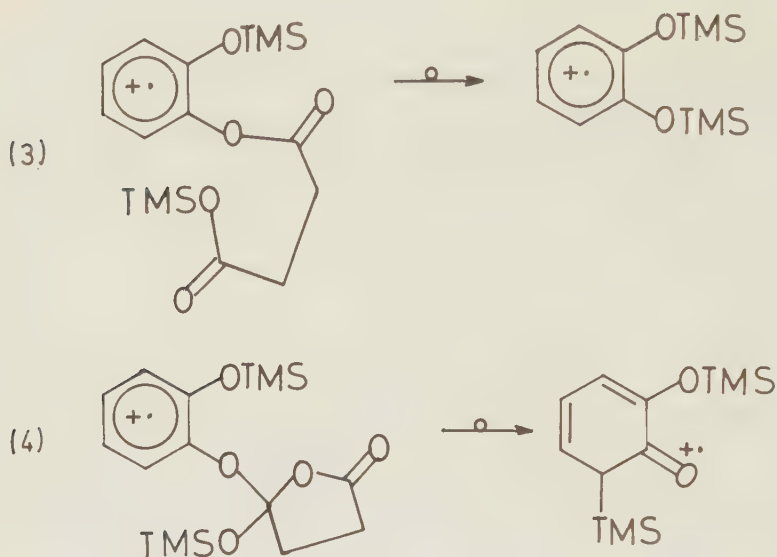
g R₁₋₄ = Me

R₄ = H

In the pH-rate profile for 12a, it was observed that at pH > 8, this compound hydrolyzed with intramolecular general base catalysis (vide infra). This phenomenon made it possible to prepare even the permethyl substituted ester 12g, which at pH 7 and 25°C has a $t_{1/2}$ = 3.3 sec.

For the unsymmetrically substituted esters, this method is supposed to give the structures formulated, i.e. 12b, c and f, because of the more rapid hydrolysis of the other isomer during the work up procedure.

The mass spectrometric behavior of the trimethylsilyl derivatives of the compounds 12a - h has also been investigated (IV) and the main feature of these derivatives under electron impact is a rearrangement involving the TMS group (Eqn. 3 and 4).



The mass spectral data for compounds 12a - h ($R = \text{TMS}$) suggest that ring-chain tautomerism may be operating in some of the parent compounds, i.e. 12f, g and h ($R = \text{H}$) (IV).

As mass spectrometric comparison between a series of catechol diacetates and compounds 4a - d shows that these compounds undergo similar fragmentation pathways. However, in contrast to the catechol diacetates, compounds 4 and their isomeric pseudoesters 5 also show processes where the molecular ions lose CO and CO_2 .

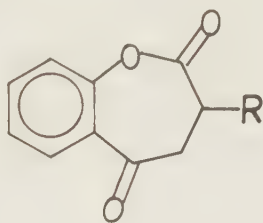
B. Kinetics of Hydrolysis of Catechol Esters

1. Cyclic succinoylcatechols, 4a - d, and catechol diacetate, 13 (II).

The pH-rate profiles for the esters 4a - d (Fig. 1) demonstrate that the water catalyzed reaction ($k_{\text{H}_2\text{O}}$) is of great importance. This behavior and also the values of the activation parameters (Table I, II) show striking similarities to what is observed for the hydrolysis of acid anhydrides²⁰.

The values of the solvent deuterium isotope effects (Table 1, II) suggest that the esters hydrolyze by general base catalysis of the attack of water by water at $\text{pH} < 7$ ²¹, while at values of pH above 7, the hydroxide ion catalyzed reaction becomes important. This change in mechanism is also reflected in the pH-rate profiles for the esters; above pH 7, the slopes of the straight lines in all cases, except one, being equal to 1.

Owing to its unsymmetrical substitution pattern, ester 4b can undergo reaction at two different rates, which implies that the values of the total rate, both for the hydroxide- and water catalyzed reactions, will be decreased. An approximate estimation of how much reaction that takes place at either carbonyl carbon atom in 4b, may be made by comparing the ratio between the rate constants for hydrolysis of the ϵ -lactones 14a and b, which under the actual reaction conditions behave similarly to the cyclic succinylcatechols.



14a $\text{R} = \text{H}$

b $\text{R} = \text{Me}$

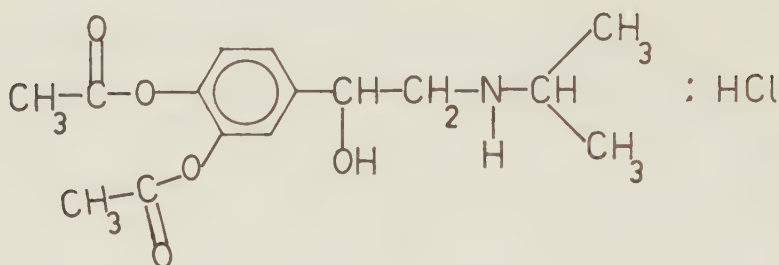
In this way it was estimated that about 70% of the reaction may take place at the unsubstituted side of the ester 4b.

From Fig. 1 it is also evident that the hydrolysis of the esters 4a - d is sensitive to steric hindrance in the succinic acid moiety, in accordance with known features of the $\text{B}_{\text{AC}}2$ mechanism for ester hydrolysis¹².

As can be seen in Fig. 1 and Table 1 (II), catechol diacetate, 13, behaves differently from its cyclic analogue 4a. Since both esters 4 and 13 have the same good leaving group²², no contribution from this has to be considered when comparing the rates of hydrolysis of these compounds. Therefore, the hydrolytic lability of the esters 4a - d compared to their non-cyclic analogues may be rationalized in terms of 1) the relatively high strain in the eight-membered ring compared to an open chain structure, 2) the inductive effect from the

adjacent ester group, and 3) conformational effect, i.e. the forced trans-conformation of the ester group in 4.

Hydrolysis of isoprenaline diacetate hydrochloride



Isoprenaline diacetate

was found to give a rate constant comparable to that of 13, which suggests that the ethanol-amino group has little or no effect on the rates of hydrolysis of esters of catecholamines (II).

2. o-Hydroxyphenyl Acid Succinates, 12a - h and Catechol Monoacetate, 15 (III and V)

The pH-rate profiles for the esters 12 and 15 are shown in Fig. 2 and 3 and relevant rate constants are summarized in Table 1 in III.

In contrast to compounds 4 and 13, both compounds 12 and 15 were found to be almost unsusceptible to intermolecular reactions of any kind. Not even such a powerful nucleophilic agent as hydroperoxide anion²³, which in the case of 4 was found to give catalytic constants ($k_{H_2O_2^-}$) of the order 10^8 M min^{-1} , significantly affected the rates of compounds 12 and 15.

A common feature of the pH-rate profiles for the esters 12a - h is found between pH 2 and ca. 8. This part of the curve can be described by Eqn. 5:

$$(5) \quad k_{\text{obsd}} = \alpha \quad k_{\alpha} = k_{\alpha} \frac{K_{\text{app}}}{(K_{\text{app}} + [\text{H}^+])}$$

where α represents the degree of ionization of the carboxyl group and k_{α} is the rate

constant for hydrolysis via intramolecular carboxylate ion attack, i.e. at the plateau of the pH-rate profile. K_{app} represents the apparent K-values for the carboxyl groups in the esters.

From Fig. 2 and 3 it is evident that increased degree of alkyl substitution in the succinic acid moiety, the gem- dimethyl effect, increases the rate of the intramolecular carboxylate ion catalyzed reaction, and the permethyl substituted ester 12g is found to hydrolyze ca. 130 times faster than 12a.

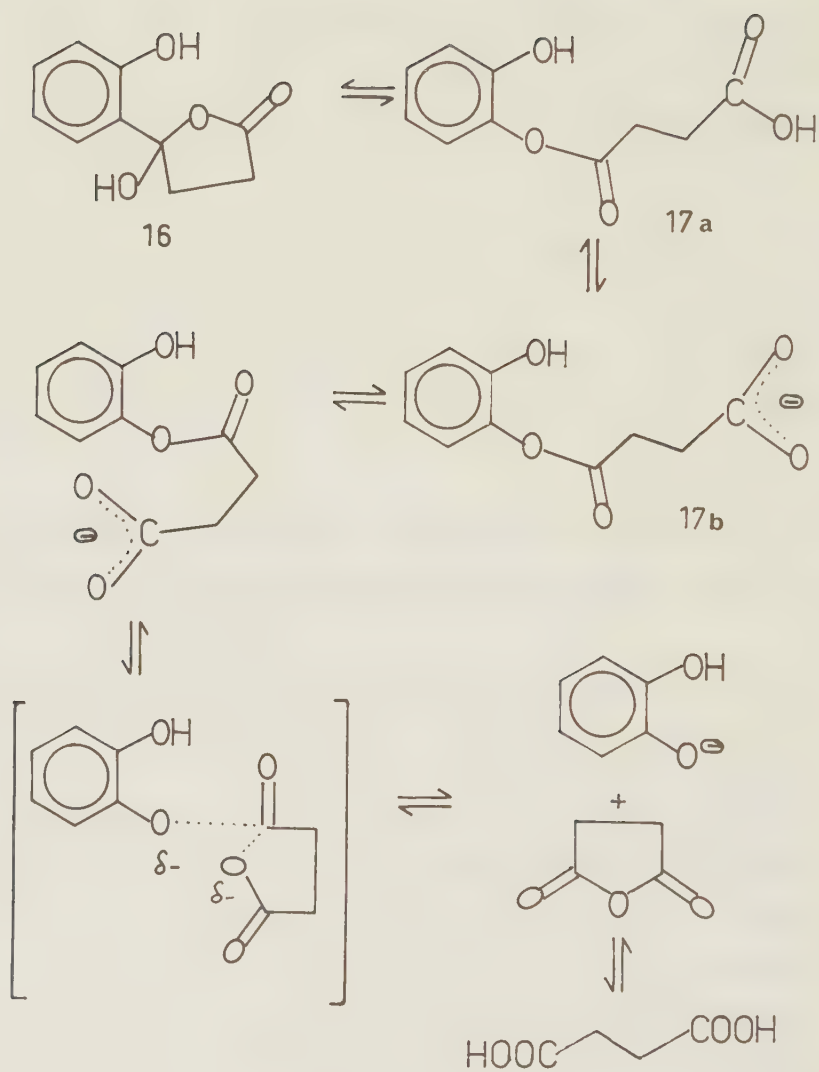
The relatively high rates of 12f and g compared to their lower homologues (see Table 2 in III) may be explained in terms of lessened solvation of the carboxylate anion, owing to a high degree of steric compression so that solvent molecules cannot be interposed ²⁴. This effect will allow a higher population of the reactive cisoid conformation of the esters.

There is some evidence for ring-chain tautomerism in the esters 12f, g and h (see above and III and IV). However, we believe that the intramolecular nucleophilic catalysis of hydrolysis of the esters 12a - h takes place via the chain form (17b) of a possible ring-chain tautomeric equilibrium (Eqn. 6). That the ring form (16) would be the reactive species is excluded, because such a mechanism should require general base catalysis of hydrolysis, and consequently show a solvent deuterium isotope effect, which in fact is not observed for any of these compounds (12) (III).

A further support for the mechanism in Eqn. 6 is that in the hydrolysis of 12h, the existence of phthalic anhydride as an intermediate was unequivocally demonstrated (see Table 1 in III).

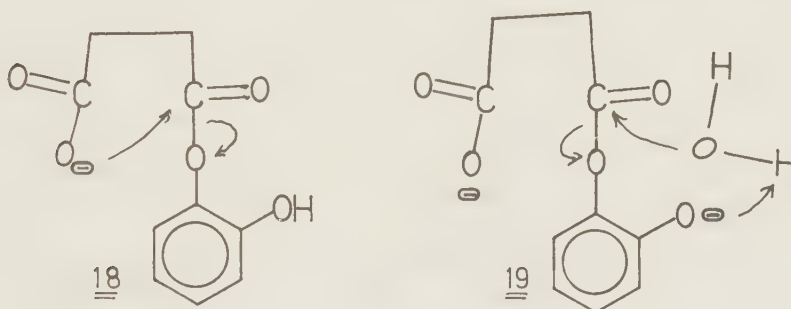
The shape of the pH-rate profiles at $pH > 8$ may be interpreted in terms of intramolecular general base catalysis of the attack of a water molecule at the ester carbonyl carbon atom from the adjacent ortho phenolate group.

The observations that the plateaus in the pH-rate profiles for 12a and 15 (Fig. 4) are found to coincide at $pH > 9$, the kinetic pK_{app} values for 12a and 15 are identical (8.6), and that catechol monobenzoate has been found to undergo hydrolysis with intramolecular general base catalysis from the adjacent ortho phenolate group ⁹, strongly support the assumption that 12a hydrolyses according to the same mechanism at $pH > 9$. Moreover, at $pH > 9$, 12a and catechol monobenzoate have identical values for the solvent deuterium isotope effect, ($k_{H_2O} / k_{D_2O} = 1.8$). That also the other esters in this series hydrolyse according to the same mechanism is evident from their pH-rate profiles at $pH > 8$, where a decrease



in rate with increased alkyl substitution is observed. The retardation of this mechanism is due to increased steric hindrance for the general base catalyzed attack of a water molecule at the ester carbonyl carbon atom. Furthermore, the pH-rate profile for 12a shows that the intramolecular carboxylate ion catalysis must be unimportant when intramolecular general base catalysis by the adjacent ortho phenolate group is operating. This is not unexpected in view of the electrostatic repulsion introduced in the dianion of 12a (V).

Thus, there is strong evidence for competing intramolecular nucleophilic and general base catalyzed mechanisms in the hydrolysis of the catechol monosuccinates 12a - g and the catechol monophthalate 12h. These mechanisms can be described by formulas 18 and 19.



Independently, it has recently been shown by Maugh II and Bruice²⁵, that this type of mechanism, and not the earlier assumed bifunctional mechanism(s), is operating in several similar systems.

The absence of intramolecular general acid catalysis from the adjacent ortho phenol group in the hydrolysis of the catechol monosuccinates is also evident from the small variation in the rates of hydrolysis of the monosuccinates of phenol, o-methoxyphenol and catechol (12a) (Table I in III).

Conclusions and Predictions

The results obtained from the kinetics of hydrolysis of compounds 4 and 12 show that the succinoyl group fulfils the three requirements stated above (p 4).

Since it is known that acylation and deacylation reactions of esterases by phenyl acetates show a normal steric order of reactivity¹³, it may be possible, by proper substitution

in the succinic acid moiety of a cyclic succinoylcatecholamine, to direct a larger concentration of the drug closer to its site of action (the receptor) without extensive inactivation of the drug by conjugating enzymes.

Further support for this assumption is found in a series of acetate esters of terbutaline (2)⁴, all of which have been found to be more effective than the parent compound (2) after peroral administration²⁶. Similar results have also been obtained for isoprenaline diacetate²⁷. These results may be interpreted in terms of a better resorption of the esters in the small intestine, together with protection of the active drug, i.e. 1d and 2, from inactivation by conjugating enzymes.

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Fig. 1

pH-rate profiles for the Hydrolysis of Cyclic Succinoylcatechols and Catechol Diacetate in 11% Acetonitrile/Water at 25.0°C.

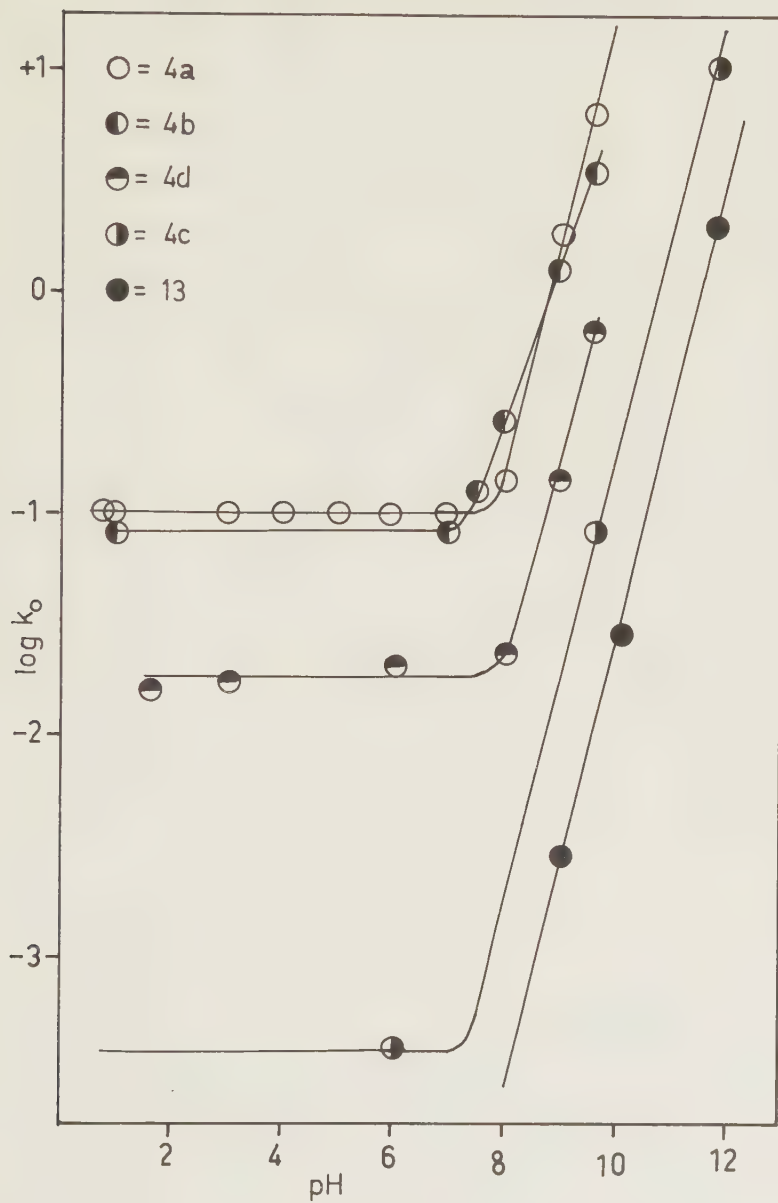


Fig. 2

pH-rate profile for the catechol monosuccinates 12a ●, 12d ○, 12g ● and for catechol monophthalate 12h ● at 25.0°C in water containing 11% (by volume) acetonitrile.

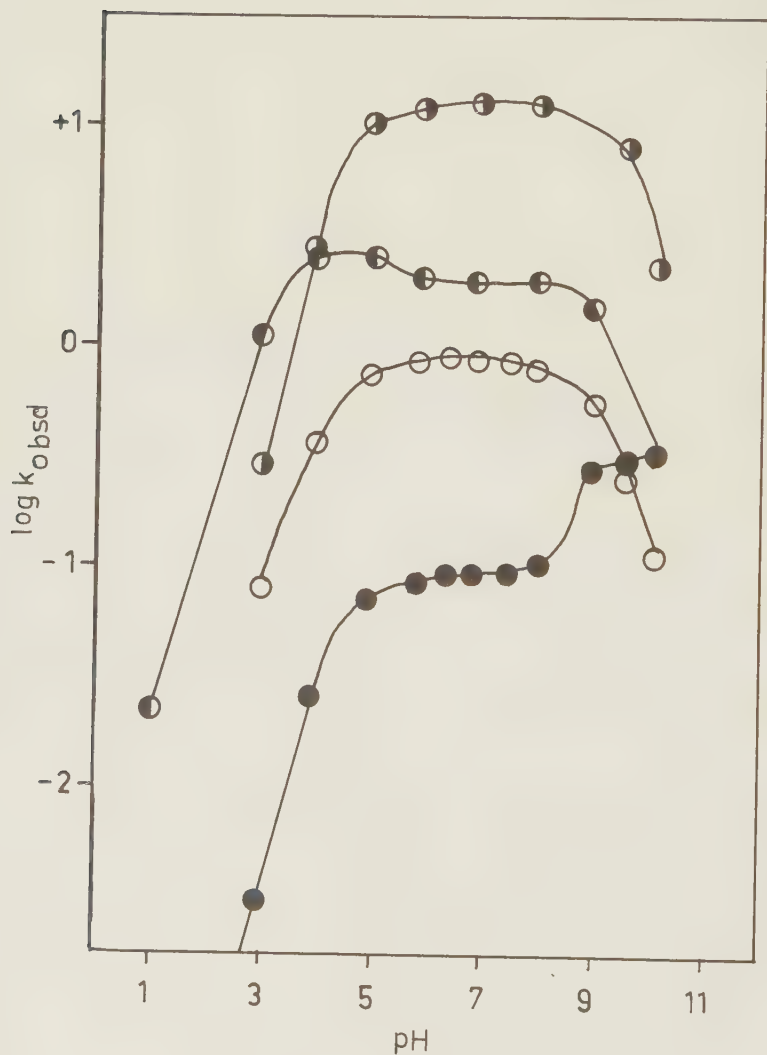


Fig. 3

pH-rate profiles for the catechol monosuccinates 12b ○, 12c ●, and 12f ◐ at 25.0°C in water containing 11% (by volume) acetonitrile.

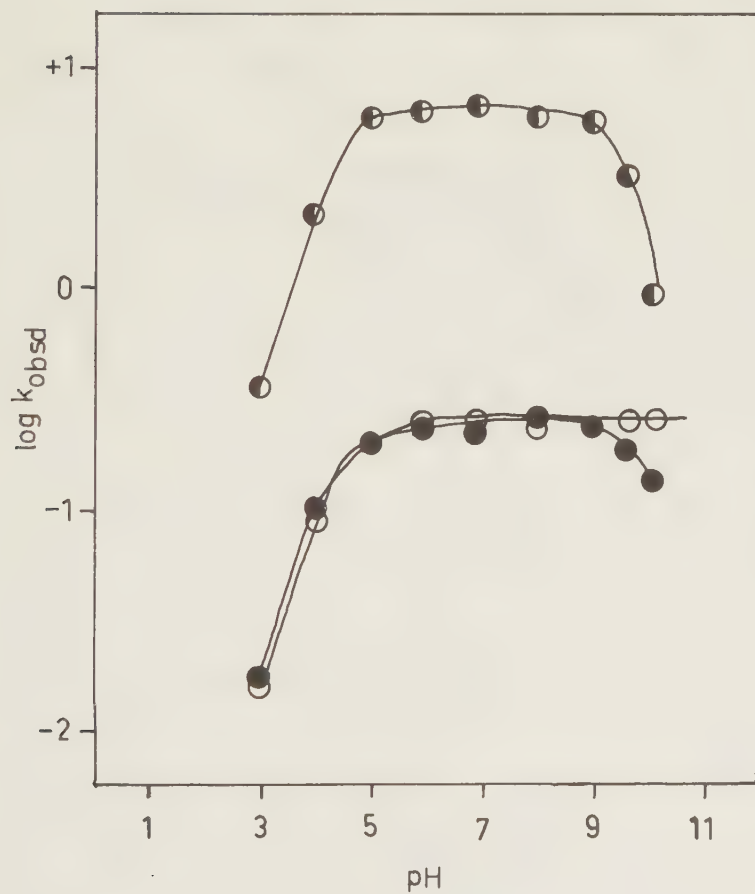
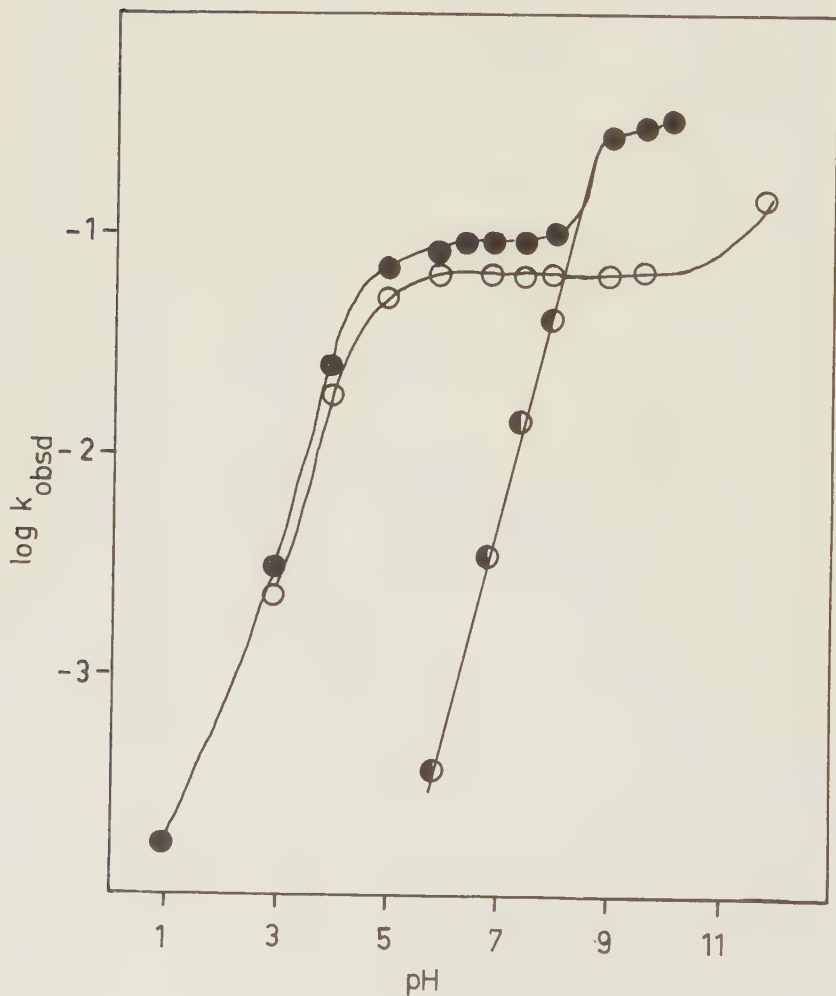


Fig. 4

pH-rate profiles for catechol monosuccinate 12a ●, o-methoxyphenyl hydrogen succinate ○, and catechol monoacetate 15 ◐ at 25.0°C in water containing 11% (by volume) acetonitrile.



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